09/ 869,360

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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4	Apr 09	ZDB will be removed from STN
NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 26	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 27	Oct 21	EVENTLINE has been reloaded
NEWS 28	Oct 24	BEILSTEIN adds new search fields
NEWS 29	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 30	Oct 25	MEDLINE SDI run of October 8, 2002
NEWS 31	Nov 18	DKILIT has been renamed APOLLIT
NEWS 32	Nov 25	More calculated properties added to REGISTRY
NEWS 33	Dec 02	TIBKAT will be removed from STN
NEWS 34	Dec 04	CSA files on STN
NEWS 35	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 36	Dec 17	TOXCENTER enhanced with additional content
NEWS 37	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 38	Dec 30	ISMEC no longer available
NEWS 39	Jan 21	NUTRACEUT offering one free connect hour in February 2003
NEWS 40	Jan 21	PHARMAML offering one free connect hour in February 2003
NEWS 41	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 42	Feb 13	CANCERLIT is no longer being updated
NEWS 43	Feb 24	METADEX enhancements
NEWS 44	Feb 24	PCTGEN now available on STN
NEWS 45	Feb 24	TEMA now available on STN
NEWS 46	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 47	Feb 26	PCTFULL now contains images

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NEWS 48 Mar 04 SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 49 Mar 19 APOLLIT offering free connect time in April 2003
NEWS 50 Mar 20 EVENTLINE will be removed from STN
NEWS 51 Mar 24 PATDPAFULL now available on STN
NEWS 52 Mar 24 Additional information for trade-named substances without structures available in REGISTRY
NEWS 53 Mar 24 Indexing from 1957 to 1966 added to records in CA/CAPLUS

NEWS EXPRESS January 6 CURRENT WINDOWS VERSION IS V6.01a, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
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FILE COVERS 1907 - 31 Mar 2003 VOL 138 ISS 14
FILE LAST UPDATED: 30 Mar 2003 (20030330/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s chymase inhibit?
907 CHYMASE

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       1558959 INHIBIT?
L1         179 CHYMASE INHIBIT?
               (CHYMASE(W)INHIBIT?)

=> s l1 and (vascular? or lipid? or vessel?)
        113727 VASCULAR?
        289585 LIPID?
        216693 VESSEL?
L2          31 L1 AND (VASCULAR? OR LIPID? OR VESSEL?)

=> d l2 1- ibib abs
YOU HAVE REQUESTED DATA FROM 31 ANSWERS - CONTINUE? Y/(N):y

L2   ANSWER 1 OF 31  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:        2002:908789  CAPLUS
TITLE:                   Effect of chymase inhibitor on
                         vascular proliferation
AUTHOR(S):               Takai, Shinji; Miyazaki, Mizuo
CORPORATE SOURCE:        Department of Pharmacology, Osaka Medical College,
                         Takatsuki City, 569-8686, Japan
SOURCE:                  Japanese Journal of Pharmacology (2002), 90(3),
                         223-227
                         CODEN: JJPAAZ; ISSN: 0021-5198
PUBLISHER:               Japanese Pharmacological Society
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   In vascular tissues, angiotensin II is potentially cleaved from
     angiotensin I by chymase and angiotensin-converting enzyme (ACE). In the
     normal state, vascular ACE regulates local angiotensin II
     formation and plays a crucial role in the regulation of blood pressure,
     whereas chymase is stored in mast cells and has no enzymic activity.
     Chymase is activated immediately upon its release into the extracellular
     matrix in vascular tissues after mast cells have been activated
     by stimuli such as vessel injury by grafting or a balloon
     catheter. In dog grafted veins, chymase activity is increased, and the
     vascular proliferation is suppressed by either a chymase
     inhibitor or an angiotensin II receptor blocker. After balloon
     injury in dog vessels, chymase activity is significantly
     increased in the injured artery, and a chymase inhibitor
     is effective in preventing the vascular proliferation, but an
     ACE inhibitor is ineffective. Chymase plays an important role in the
     development of vascular proliferation via the induction of local
     angiotensin II formation in injured vessels.
REFERENCE COUNT:         35    THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2   ANSWER 2 OF 31  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:        2002:813662  CAPLUS
DOCUMENT NUMBER:         138:101146
TITLE:                   Suppression of basic fibroblast growth factor-induced
                         angiogenesis by a specific chymase
                         inhibitor, BCEAB, through the
                         chymase-angiotensin-dependent pathway in hamster
                         sponge granulomas
AUTHOR(S):               Muramatsu, Michiko; Yamada, Mayumi; Takai, Shinji;
                         Miyazaki, Mizuo
CORPORATE SOURCE:        Department of Pharmacology, Osaka Medical College,
                         Takatsuki City, 569-8686, Japan
SOURCE:                  British Journal of Pharmacology (2002), 137(4),
                         554-560
                         CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER:               Nature Publishing Group
DOCUMENT TYPE:           Journal
```

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LANGUAGE: English

AB The authors investigated the profound involvement of mast cell chymase, an alternative angiotensin II-generating enzyme, in angiogenesis using a specific **chymase inhibitor**. The authors also studied the functional profiles of this novel inhibitor in basic fibroblast growth factor (bFGF)-induced angiogenesis. In this study, angiogenesis was induced by daily injections of bFGF (0.3 .mu.g site-1 day-1), angiotensin I (2 nmol site-1 day-1) or angiotensin II (2 nmol site-1 day-1) into sponges implanted to male hamsters s.c. for 7 days. Angiogenesis in the granulation tissue surrounding sponges was evaluated by measuring the Hb content and local blood flow as the parameters for angiogenesis. A **chymase inhibitor**, BCEAB (4-[1-{[bis-(4-methyl-phenyl)-methyl]-carbamoyl}-3-(2-ethoxybenzyl)-4-oxo-azetidine-2-yloxy]-benzoic acid), was simultaneously administered into the implanted sponges (2 or 5 nmol site-1 day-1, for 7 days) treated with bFGF and strongly suppressed the Hb contents in sponge granulomas. In the studies using a laser doppler perfusion imager, BCEAB (5 nmol site-1 day-1) also attenuated the bFGF-induced increase of local blood flow around the implanted sponge granuloma. In bFGF-induced angiogenesis, chymase activity in sponge granulomas was substantially increased. It was also confirmed that the chymase activity increased by bFGF was significantly and dose-dependently inhibited by BCEAB (2, 5 nmol site-1 day-1). BCEAB inhibited the Hb contents and the expression of **vascular** endothelial growth factor (VEGF) mRNA induced by angiotensin I but not by angiotensin II. These results suggest that the significance of chymase in bFGF-induced angiogenesis was confirmed, and a novel inhibitor, BCEAB, strongly suppresses the bFGF-induced angiogenesis through the chymase-angiotensin II-VEGF dependent pathway.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 31 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:761196 CAPLUS

TITLE: Lengthy suppression of **vascular** proliferation by a **chymase inhibitor** in dog grafted veins

AUTHOR(S): Tsunemi, Koutaro; Takai, Shinji; Nishimoto, Masayoshi; Yuda, Atsushi; Jin, Denan; Sakaguchi, Masato; Sawada, Yoshihide; Asada, Kunio; Kondo, Keiichiro; Sasaki, Shinjira; Miyazaki, Mizuo

CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Osaka, 569-8686, Japan

SOURCE: Journal of Thoracic and Cardiovascular Surgery (2002), 124(3), 621-625
CODEN: JTCSAQ; ISSN: 0022-5223

PUBLISHER: Mosby, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Unavailable

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 31 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:642039 CAPLUS

DOCUMENT NUMBER: 138:36705

TITLE: The role of chymase in **vascular** proliferation

AUTHOR(S): Takai, Shinji; Miyazaki, Mizuo

CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki City, Osaka, 569-8686, Japan

SOURCE: Drug News & Perspectives (2002), 15(5), 278-282
CODEN: DNPEED; ISSN: 0214-0934

PUBLISHER: Prous Science

DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. In **vascular** tissues, angiotensin II is potentially cleaved from angiotensin I by chymase and angiotensin-converting enzyme (ACE). Chymase is stored in mast cells and has no enzymic activity in the normal state. Chymase is activated immediately upon its release into the extracellular matrix in **vascular** tissues after mast cells have been activated by stimuli such as **vessel** injury by grafting or a balloon catheter. In dog grafted veins, chymase activity is increased, and the **vascular** proliferation is suppressed by either a **chymase inhibitor** or an angiotensin II receptor blocker. After balloon injury in dog **vessels**, chymase activity is locally increased in the injured artery, and a **chymase inhibitor** is effective in preventing the **vascular** proliferation, but an ACE inhibitor is ineffective. Chymase plays an important role in the development of **vascular** proliferation via the induction of local angiotensin II formation in injured **vessels**.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 5 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:634986 CAPLUS
TITLE: **Chymase inhibition** suppresses high-cholesterol diet-induced **lipid** accumulation in the hamster aorta
AUTHOR(S): Uehara, Yoshinari; Urata, Hidenori; Ideishi, Munehito; Arakawa, Kikuo; Saku, Keijiro
CORPORATE SOURCE: Department of Internal Medicine, Fukuoka University School of Medicine, Jonan-ku, Fukuoka, 814-0180, Japan
SOURCE: Cardiovascular Research (2002), 55(4), 870-876
CODEN: CVREAU; ISSN: 0008-6363
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: The role of chymase (a mast cell-derived angiotensin II-forming serine proteinase) in aortic **lipid** deposition was investigated using an orally active, non-peptide **chymase inhibitor**, SUN-C8257. Methods: Male golden Syrian hamsters, 8 wk old, were fed with a std. rodent meal supplemented with or without 0.5% cholesterol and 10% coconut oil for 12 wk. The hamsters fed high cholesterol diet were further sepd. into two groups treated with or without SUN-C8257 for 12 wk. The aortic **lipid** deposition was visualized by Oil red O staining and planimetrically measured. Immunohistochem. staining for angiotensin II (Ang II) of the aortic root region was performed. Aortic Ang II-forming activity was measured using Ang I as a substrate. Plasma total-, low-d. lipoprotein (LDL)-, high-d. lipoprotein (HDL)-cholesterol and triglyceride were quantified by enzymic methods. Plasma Ang I and Ang II were measured by RIA. Results: After 12 wk of high cholesterol diet, aortic chymase activity in the untreated group increased significantly and showed a pos. correlation with plasma total- and LDL-cholesterol. This group of hamsters developed marked **lipid** deposits in the aortic intima. However, treatment with SUN-C8257 significantly suppressed aortic **lipid** deposition without changing body wt., blood pressure, plasma LDL-cholesterol and Ang II levels. The level of the adventitial Ang II-immunoreactivity was markedly inhibited in the group treated with SUN-C8257. Conclusion: Our results suggest that arterial chymase may participate in the acceleration of **lipid** deposition in arterial walls exposed to high plasma cholesterol and that inhibition of arterial chymase may retard the progression of atherosclerosis.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 31 CAPLUS COPYRIGHT 2003 ACS

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ACCESSION NUMBER: 2002:441530 CAPLUS
DOCUMENT NUMBER: 137:260705
TITLE: Alternate angiotensin II-forming pathways and their importance in physiological or physiopathological conditions
AUTHOR(S): Monteiro de Resende, Micheline; Mill, Jose Geraldo
CORPORATE SOURCE: Dep. Physiological Sci., Centro Biomedico da UFES, Brazil
SOURCE: Arquivos Brasileiros de Cardiologia (2002), 78(4), 425-438
CODEN: ABCAAJ; ISSN: 0066-782X
PUBLISHER: Sociedade Brasileira de Cardiologia
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Portuguese/English
AB A review. Topics discussed include: chymase (a serine proteinase that is capable of cleaving angiotensin I into angiotensin II) in the heart and blood **vessels**, differences between species in the generation of angiotensin II, studies in the intact kidney, chymase in cardiomyopathies, and **chymase inhibition**. A complete English version is provided.
REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 7 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:371857 CAPLUS
DOCUMENT NUMBER: 137:166726
TITLE: Effects of chymase on human dermal microvascular endothelial cells and human dermal fibroblasts
AUTHOR(S): Tanabe, Yuko; Soma, Yoshinao; Takai, Shinji; Miyazaki, Mizuo; Mizoguchi, Masako
CORPORATE SOURCE: Dep. Dermatol., St. Marianna Univ. Sch. Med., Kawasaki, 216-8511, Japan
SOURCE: Nippon Hifuka Gakkai Zasshi (2002), 112(3), 239-246
CODEN: NHKZAD; ISSN: 0021-499X
PUBLISHER: Nippon Hifuka Gakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Chymase is a proteolytic enzyme present in mast cell granules that is released by mast cell degranulation with tryptase, histamines, and other mediators. To elucidate the roles of mast cells in various biol. processes, including fibrosis and wound repair, it is necessary to know the effects of chymase on fibroblasts and **vascular** endothelial cells. We examd. the effect of human chymase on human dermal microvascular endothelial cells (HDMEC) and human dermal fibroblasts (HDF). Chymase did not affect HDMEC growth, but it did stimulate the proliferation of HDF at 1 nM concn. This growth-promoting activity was completely inhibited by the addn. of the chymase substrate peptide, Suc-Val-Pro-PheP(OPh)2. Chymase did not have any effect on ICAM-1 or VCAM-1 expression in HDMEC and HDF. The present study suggests that the mitogenic effect of chymase released from mast cells on dermal fibroblasts may be involved in some pathol. and physiol. processes. Another **chymase inhibitory** agent, which is a quinazoline deriv., stimulated the growth of HDMEC and enhanced VCAM-1 expression in the cells, suggesting an angiogenic effect.

L2 ANSWER 8 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:314922 CAPLUS
DOCUMENT NUMBER: 136:335238
TITLE: Novel remedies or preventives for angiostenosis
INVENTOR(S): Miyazaki, Mizuo; Kamoshita, Keiichi; Sukenaga, Yoshikazu; Suzuki, Yoshikazu
PATENT ASSIGNEE(S): Nippon Kayaku Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 35 pp.

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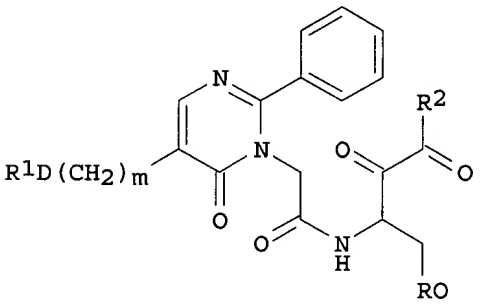
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002032881	A1	20020425	WO 2001-JP9131	20011018
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001095952	A5	20020429	AU 2001-95952	20011018

PRIORITY APPLN. INFO.: JP 2000-318832 A 20001019
JP 2001-282509 A 20010918
WO 2001-JP9131 W 20011018

OTHER SOURCE(S): MARPAT 136:335238
GI



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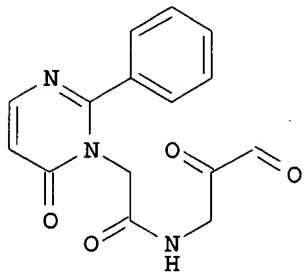


II

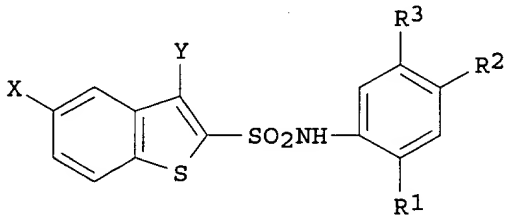
AB Remedies or preventives for angiostenosis which comprise as the active ingredient a compd. having a pyrimidone skeleton and having a **chymase inhibitory** activity, for example, a compd. having the skeleton structure represented by the following formula (II): and having a highly selective chymase activity or its pharmacol. acceptable salt. These drugs are characterized by being usable in oral administration.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 9 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:220571 CAPLUS
DOCUMENT NUMBER: 136:263085
TITLE: Preparation of N-phenylbenzothiophenesulfonamide derivatives as selective **chymase inhibitors**
INVENTOR(S): Satoh, Shoji; Tatsui, Akira; Hasegawa, Takeshi; Yamada, Hideki; Kazayama, Shin-ichi; Morita, Takahiro; Masaki, Hidekazu; Takahashi, Atsuo
PATENT ASSIGNEE(S): Toa Eiyo Ltd., Japan
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002022595	A1	20020321	WO 2001-JP8061	20010917
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001088053	A5	20020326	AU 2001-88053	20010917

PRIORITY APPLN. INFO.: JP 2000-282046 A 20000918
JP 2001-122972 A 20010420
WO 2001-JP8061 W 20010917
OTHER SOURCE(S): MARPAT 136:263085
GI



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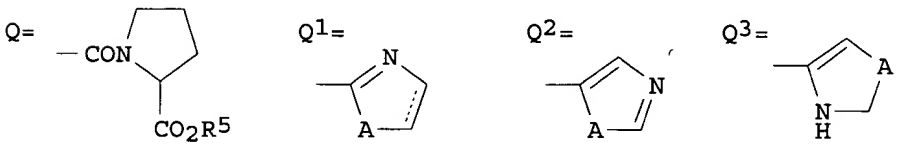

AB Novel N-substituted benzothiophenesulfonamide derivs. represented by the general formula [I; X = H,halo, lower alkyl; Y = lower alkyl; R1, R2 = H, lower alkoxycarbonyl, lower alkylsulfonyl, benzoyl, C1-4 acyl, lower alkoxy, lower alkoxycarbonylmethylthioacetyl, NO2, CONHR4 [wherein R4 = H, lower alkoxycarbonylmethyl, carboxymethyl, CH(CH2OH)CO2R5 (wherein R5 = H, lower alkyl)], Q, Q1, Q2, Q3 (wherein A = O, S, NH; the dotted line represents a single or double bond); R3 = H, lower alkoxy, lower alkyl] or salts thereof are prepd. These compds. are useful as preventives and

remedies for cardiocirculatory diseases caused by hyperprodn. of angiotensin II or endothelin I based on chymase activity which have an effect of selectively inhibiting chymase. In particular they are useful for the prevention and/or treatment of myocardial infarction, restenosis after percutaneous transluminal coronary angioplasty (PTCA), or thickening of inner coat (endosporium) after bypass graft. Thus, N-[4-[(5-fluoro-3-methylbenzo[b]thiophen-2-ylsulfonyl)amino]-3-(methanesulfonyl)benzoyl]-L-serine Me ester was stirred with Burgess reagent in THF at 60.degree. for 2 h to give 2-[4-[(5-fluoro-3-methylbenzo[b]thiophen-2-ylsulfonyl)amino]-3-(methanesulfonyl)phenyl]-4,5-dihydrooxazole-4-carboxylic acid Me ester which was treated with bromotrichloromethane and DBU in CH2Cl2 at -20.degree. for 5 min and 0.degree. for 3.5 h to give 2-[4-[(5-fluoro-3-methylbenzo[b]thiophen-2-ylsulfonyl)amino]-3-(methanesulfonyl)phenyl]oxazole-4-carboxylic acid Me ester. Alkali hydrolysis of the latter ester with a mixt. of 10% aq. NaOH, MeOH, and THF at room temp. for 17 h followed by distn. of the solvent and acidification with 1 M aq. HCl gave 2-[4-[(5-fluoro-3-methylbenzo[b]thiophen-2-ylsulfonyl)amino]-3-(methanesulfonyl)phenyl]oxazole-4-carboxylic acid (II). II showed IC50 of 2, >10,000, and >10,000 nmol/L against chymase, chymotrypsin, and cathepsin G, resp.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 10 OF 31 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:2957 CAPLUS

DOCUMENT NUMBER: 136:181705

TITLE: Mast cell **chymase inhibits** smooth muscle cell growth and collagen expression in vitro: transforming growth factor-.beta.1-dependent and -independent effects

AUTHOR(S): Wang, Yenfeng; Shiota, Naotaka; Leskinen, Markus J.; Lindstedt, Ken A.; Kovanen, Petri T.

CORPORATE SOURCE: Wihuri Res. Inst., Helsinki, 00140, Finland

SOURCE: Arteriosclerosis, Thrombosis, and Vascular Biology (2001), 21(12), 1928-1933
CODEN: ATVBFA; ISSN: 1079-5642

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In the vulnerable areas of fibrous caps of advanced atherosclerotic lesions, chymase-contg. mast cells are present. In such areas, the nos. of smooth muscle cells (SMCs) and the content of collagen are reduced. In this in vitro study, we found that the addn. of chymase, isolated and purified from rat serosal mast cells, to cultured rat aortic SMCs of the synthetic phenotype (s-SMCs) inhibited their proliferation by blocking the G0/G1.fwdarw.S transition in the cell cycle. Rat chymase and recombinant human **chymase inhibited** the expression of collagen type I and type III mRNA in s-SMCs and in human coronary arterial SMCs. The growth-inhibitory effect of chymase was partially reversed by addn. to the culture medium of an antibody capable of neutralizing the activity of transforming growth factor-.beta.1 (TGF-.beta.1). Immunocytochem. showed that the s-SMCs expressed and synthesized extracellular matrix-assocd. TGF-.beta.1. On exposure to mast cell chymase, the extracellular matrix-assocd. latent TGF-.beta.1 was released and activated. as demonstrated by immunoblotting and by an ELISA with TGF-.beta.1 type II receptor for capture. When added to s-SMCs. such chymase-released TGF-.beta.1 was capable of inhibiting their growth. In contrast, the inhibitory effect of chymase on collagen synthesis by s-SMCs did not depend on TGF-.beta.1. Taken together, the findings support the hypothesis that chymase released from activated mast cells in atherosclerotic plaques contributes to cap remodeling.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 11 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:749558 CAPLUS
DOCUMENT NUMBER: 136:15646
TITLE: Significance of chymase-dependent angiotensin II-forming pathway in the development of **vascular** proliferation
AUTHOR(S): Nishimoto, Masayoshi; Takai, Shinji; Kim, Shokei; Jin, Denan; Yuda, Atsushi; Sakaguchi, Masato; Yamada, Mayumi; Sawada, Yoshihide; Kondo, Keiichiro; Asada, Kunio; Iwao, Hiroshi; Sasaki, Shinjiro; Miyazaki, Mizuo
CORPORATE SOURCE: Dep. Pharmacol., Osaka City Univ. Med. Sch., Osaka, Japan
SOURCE: Circulation (2001), 104(11), 1274-1279
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Vascular** tissues of humans and dogs contain chymase as an angiotensin II-forming enzyme. In this study, the authors investigated whether chymase-dependent angiotensin II formation plays a crucial role in the development of **vascular** proliferation in dog grafted veins. The right external jugular vein of dogs was grafted to the ipsilateral carotid artery. As a control group. the right external jugular veins in dogs that had not received grafts were used. In the **chymase inhibitor**-treated group, the vein was infiltrated with 10 .mu.M Suc-Val-Pro-PheP(OPh)2 and was grafted to the carotid artery. In the placebo-treated group, ACE activity in the grafted veins was significantly lower than that in the control veins up to 7 days after the operation, whereas chymase activity was increased significantly. After 7 days, the mRNA levels of collagen I, collagen III, and fibronectin, all of which are induced by an increase of angiotensin II action, were significantly increased in the grafted veins, and the intima-media ratio of the grafted veins was also increased. In the **chymase inhibitor** -treated group, the chymase activity in the grafted veins 7 days after the operation was suppressed to 12.1%. The elevated mRNA levels of fibronectin, collagen I, and collagen III in the grafted veins were significantly suppressed by treatment with the **chymase inhibitor**, and the intima-media ratio was also decreased significantly. The authors demonstrate for the first time that chymase-dependent angiotensin II formation plays an important role in the development of **vascular** proliferation in the grafted veins.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 12 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:669762 CAPLUS
DOCUMENT NUMBER: 136:63818
TITLE: Oral administration of a specific **chymase inhibitor**, NK3201, inhibits **vascular** proliferation in grafted vein
AUTHOR(S): Takai, Shinji; Jin, Denan; Nishimoto, Masayoshi; Yuda, Atsushi; Sakaguchi, Masato; Kamoshita, Keiichi; Ishida, Koichi; Sukenaga, Yoshikazu; Sasaki, Shinjiro; Miyazaki, Mizuo
CORPORATE SOURCE: Departments of Pharmacology, Osaka Medical College, Osaka, 569-8686, Japan
SOURCE: Life Sciences (2001), 69(15), 1725-1732
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

09/ 869,360

AB Chymase may play an important role in **vascular** proliferation, as shown by in-vitro expts., but the role of chymase in vivo has been unclear. In this study, we investigated the effect of a novel **chymase inhibitor**, NK3201, on this proliferation in dog grafted veins. NK3201 inhibited human and dog chymases, but not rabbit ACE. NK3201 suppressed the Ang I-induced **vascular** contraction in isolated dog arteries in the presence of an ACE inhibitor, and the IC50 value of chymostatin and NK3201 in dog artery was 320 nM. In dog, the concn. of NK3201 in blood was about 10 .mu.M at 24 h after oral administration of the drug (5 mg/kg). In the group treated with NK3201, each dog was administered orally 5 mg/kg per day from 5 days before to the day before the removal of the grafted veins. Each dog underwent right common carotid artery bypass grafting with the ipsilateral external jugular vein. By 28 days after grafting, a significant **vascular** proliferation was obsd. in the grafted veins and the chymase activity was also increased significantly. Treatment with **chymase inhibitor** significantly suppressed the proliferation of the grafted veins and the increased chymase activity. In this study, we demonstrate for the first time that oral administration of a specific **chymase inhibitor**, NK3201, appears useful for preventing **vascular** proliferation.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 13 OF 31 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:647377 CAPLUS

DOCUMENT NUMBER: 135:339779

TITLE: Functional evidence for a role of **vascular** chymase in the production of angiotensin II in isolated human arteries

AUTHOR(S): Richard, Vincent; Hurel-Merle, Sonia; Scalbert, Elizabeth; Ferry, Gilles; Lallemand, Francoise; Bessou, Jean-Paul; Thuillez, Christian

CORPORATE SOURCE: INSERM E9920 (IFRMP23), Rouen University Medical School, Rouen, 76183, Fr.

SOURCE: Circulation (2001), 104(7), 750-752
CODEN: CIRCAZ; ISSN: 0009-7322

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In human arteries, angiotensin-converting enzyme (ACE) inhibitors incompletely block the prodn. of angiotensin (Ang) II from Ang I. This ACE-independent prodn. of Ang II appears to be caused by serine proteases, one of which presumably is chymase. However, several serine proteases may produce Ang II, and the exact role of chymase in the **vascular** prodn. of Ang II has never been directly evaluated using selective **chymase inhibitors**. Rings of human mammary arteries were subjected to either Ang I or the chymase-selective substrate [Pro11,D-Ala12] Ang I in the absence or the presence of the ACE inhibitor captopril, the serine protease inhibitor chymostatin, or the selective **chymase inhibitor** C41. Captopril only partially inhibited (by 33%) the response to Ang I. In the absence of captopril, C41 markedly reduced (by 44%) the response to Ang I, and this effect was identical to that of chymostatin. C41 also significantly reduced the response to Ang I in the presence of captopril, although this inhibitory effect was slightly less than that of captopril in combination with chymostatin. [Pro11,D-Ala12] Ang I induced potent contractions that were not affected by captopril but were abolished by chymostatin and markedly reduced by C41. In addn., the authors found that prior treatment of the patients with an ACE inhibitor did not affect the in vitro response to Ang I (in the absence or the presence of captopril) or to [Pro11,D-Ala12] Ang I. In conclusion, the authors' results reinforce the hypothesis that chymase is a major serine protease implicated in the ACE-independent

prodn. of Ang II in human arteries.
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 14 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:486784 CAPLUS
DOCUMENT NUMBER: 135:205606
TITLE: Local angiotensin II-generating system in **vascular** tissues: The roles of chymase
AUTHOR(S): Miyazaki, Mizuo; Takai, Shinji
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki, 569-8686, Japan
SOURCE: Hypertension Research (2001), 24(3), 189-193
CODEN: HRESE4; ISSN: 0916-9636
PUBLISHER: Japanese Society of Hypertension
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 47 refs., of the roles of angiotensin II-producing enzymes. In **vascular** tissues, angiotensin II is potentially cleaved from angiotensin I by angiotensin converting enzyme (ACE) and chymase. It has been confirmed that **vascular** tissues of humans, monkeys, dogs and hamsters have a chymase-dependent angiotensin II-forming pathway. Much like other hypertensive models, hamster hypertensive models show high levels of **vascular** ACE activity, but not chymase activity. In hypertensive hamsters, administration of either an ACE inhibitor or an angiotensin II type 1 (AT1) receptor antagonist resulted in similar redns. in blood pressure, suggesting that chymase is not involved in the maintenance of high blood pressure in this model. In monkeys fed a high-cholesterol diet, ACE activity was increased in the atherosclerotic lesions, and an ACE inhibitor and an AT1 receptor antagonist prevented atherosclerosis to a similar degree, suggesting that ACE may be mainly involved in the development of atherosclerosis. After balloon injury in dog **vessels**, both ACE and chymase activities were locally increased about 3-fold in the injured arteries, and an AT1 receptor antagonist was effective in preventing the intimal formation, but an ACE inhibitor was ineffective. In dog grafted veins, the activities of chymase were increased 15-fold, but those of ACE were increased only 2-fold, and the intimal formation was suppressed by either an AT1 receptor antagonist or a **chymase inhibitor**. In the normal **vascular** tissues, ACE plays a crucial role for angiotensin II prodn., whereas chymase is stored in mast cells in an inactive form. Chymase acquires the ability to form angiotensin II following mast cells activation followed by mast cells activation by a strong stimulus such as occurs in catheter-injury or grafting. Together, these results indicate that chymase plays a major role in the **vascular** angiotensin II-generating system, particularly in cases of **vascular** injury.
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 15 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:338384 CAPLUS
DOCUMENT NUMBER: 134:348278
TITLE: Inhibitors against **vascular lipid** deposition containing **chymase-inhibiting** substances
INVENTOR(S): Fukami, Harukazu; Urata, Hidenori
PATENT ASSIGNEE(S): Suntory Limited, Japan
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032214	A1	20010510	WO 2000-JP7706	20001101
W: AU, CA, CN, HU, JP, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
CA 2358314	AA	20010510	CA 2000-2358314	20001101
EP 1142586	A1	20011010	EP 2000-971729	20001101
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: JP 1999-311257 A 19991101
WO 2000-JP7706 W 20001101

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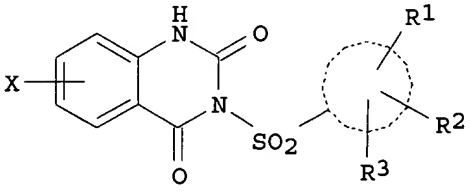

I

AB Preventive or therapeutic agents for diseases accompanied with **vascular** function disorders related to deposition of **lipid** on **vessel** walls, contg. specific **chymase inhibitors** as the active ingredient. Quinazoline derivs. of general formula (I) are usable as the specific **chymase inhibitor**. In said formula, A is an arom. ring.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 16 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:247309 CAPLUS
DOCUMENT NUMBER: 134:280845
TITLE: Preparation of acylsulfonamide derivatives as **chymase inhibitors**
INVENTOR(S): Aoyama, Yukio; Seki, Maki; Masuda, Hirokazu; Usui, Yoshihiro; Abe, Yuji; Shimada, Mayumi; Yamamoto, Mutsuya
PATENT ASSIGNEE(S): Mitsubishi Chemical Corporation, Japan
SOURCE: PCT Int. Appl., 259 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001023349	A1	20010405	WO 2000-JP6695	20000928
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: JP 1999-278374 A 19990930
JP 1999-278375 A 19990930
JP 1999-278377 A 19990930
JP 1999-278378 A 19990930
JP 1999-278379 A 19990930

OTHER SOURCE(S): MARPAT 134:280845

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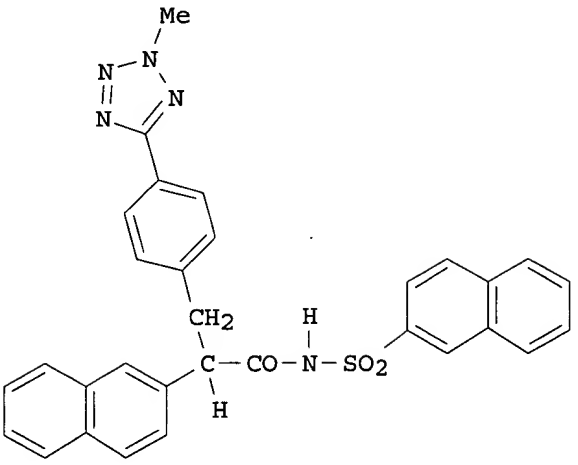

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AB The title compds. R1CH[(CH2R2)n](NH)mCONHSO2R3 [R1 = (un)substituted heterocyclyl, etc.; n = 1 -4; m = 0 or 1; R2 = (un)substituted heterocyclyl, etc.; when R2 is (un)substituted aryl, R3 is (un)substituted naphthyl, heterocyclyl; when R2 is (un)substituted heterocyclyl, R3 is (un)substituted Ph, naphthyl, heterocyclyl] are prepd. The title compds. are useful as remedies for hypertension. The title compd. I in vitro showed IC50 of 0.66 .mu.M against chymase.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 17 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:78369 CAPLUS
DOCUMENT NUMBER: 134:131554
TITLE: Preparation of novel thiazine or pyrazine derivatives as **chymase inhibitors**
INVENTOR(S): Matsumoto, Junzo; Nishimura, Kazuo; Ban, Masakazu; Fujimura, Ken-ichi; Kobayashi, Naoyuki; Hori, Masanori; Honda, Takahiro
PATENT ASSIGNEE(S): Santen Pharmaceutical Co., Ltd., Japan; Matsumoto, Eiko
SOURCE: PCT Int. Appl., 278 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007419	A1	20010201	WO 2000-JP4964	20000726

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,

LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 2000063141	A5	20010213	AU 2000-63141	20000726
JP 2001097957	A2	20010410	JP 2000-224667	20000726
EP 1211249	A1	20020605	EP 2000-949890	20000726

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL

PRIORITY APPLN. INFO.: JP 1999-210907 A 19990726
WO 2000-JP4964 W 20000726

OTHER SOURCE(S): MARPAT 134:131554

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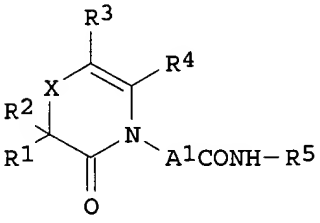

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AB Novel compds. having as the main skeleton 3-oxo-3,4-dihydro-2H-1,4-thiazine or 2-oxo-1,2,3,4-tetrahydropyrazine, which are represented by general formula [I; wherein X = S, R6-(A2)n-N; R1, R2 = H, lower alkyl, cycloalkyl, cycloalkyl, aryl; R3, R4 = H, lower alkyl, cycloalkyl, aryl, heteroaryl; R5 = H, lower alkyl, cycloalkyl, aryl, A3-A4-R7; wherein R6 = H, lower alkyl, cycloalkyl, HO, lower alkoxy, aryl, aryloxy, heteroaryl; R7 = H, lower alkyl, HO, lower alkoxy, aryl, aryloxy, NH2, lower alkylamino, arylamino, arom. or nonarom. heterocyclyl; n = 0,1; A1 = lower alkylene; A2 = CO, SO2; A3 = lower alkylene; A4 = CO, oxalyl; the above lower alkyl is optionally substituted by halo, HO, lower alkoxy, aryl, or aryloxy; the above lower alkoxy or lower alkylene is optionally substituted by aryl], are prepd. These compds. are useful for the treatment of chymase-related diseases such as myocardial infarction, heart failure, **vascular** restenosis after PTCA, hypertension, diabetes complications, allergies, and asthma. (3S)-3-[[[[(3R)-4-benzoyl-3-isopropyl-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrazin-1-yl]methyl]carbonyl]amino]-2-oxo-4-phenylbutanoic acid iso-Pr ester which showed IC50 of 0.20 .times. 10-6 M against chymase.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 18 OF 31 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:9249 CAPLUS
DOCUMENT NUMBER: 134:66707
TITLE: The functional ratio of chymase and angiotensin converting enzyme in Angiotensin I-induced **vascular** contraction in monkeys, dogs and rats
AUTHOR(S): Jin, Denan; Takai, Shinji; Yamada, Mayumi; Sakaguchi, Masato; Miyazaki, Mizuo
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki City, 569-8686, Japan
SOURCE: Japanese Journal of Pharmacology (2000), 84(4), 449-454
CODEN: JJPAAZ; ISSN: 0021-5198
PUBLISHER: Japanese Pharmacological Society

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recently, a chymase-dependent angiotensin (Ang) II-forming pathway was found in human cardiovascular tissues, and the significance of this pathway in the pathogenesis of some cardiovascular diseases was suggested. The present study examd. the ratio of angiotensin converting enzyme (ACE) to chymase-dependent Ang II formation in various isolated **vessels** from monkeys, dogs and rats. In all of the examd. **vessels**, the addn. of KCl at a concn. of 50 mM could induce a maximal contraction. Except for monkey coronary artery and rat renal and femoral artery, the addn. of Ang I could induce transitory contractions, whereas the force of contractions in these **vessels** was quite different. The sensitivity to Ang II in these **vessels** was similar to that for Ang I. In monkey gastroepiploic and mesenteric arteries, about 70% of the Ang I-induced contraction was suppressed by **chymase inhibition**, while it was suppressed about 50% in monkey renal, femoral and carotid arteries. In dog renal arteries, about 65% of the Ang I-induced contraction was suppressed by **chymase inhibition**, while it was suppressed by about 30% in other dog arteries. In contrast, in all rat arteries, Ang I-induced contractions were completely suppressed by treatment with ACE inhibitor alone. We concluded that regional differences in the response to Ang I exist in **vascular** tissues, and the ratio of ACE- to chymase-dependent Ang II formation is different in the various **vessels**.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 19 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:774311 CAPLUS
DOCUMENT NUMBER: 134:220442
TITLE: Hypothesis regarding the pathophysiological role of alternative pathways of angiotensin II formation in atherosclerosis
AUTHOR(S): Arakawa, Kikuo; Urata, Hidenori
CORPORATE SOURCE: Department of Internal Medicine, School of Medicine, Fukuoka University, Fukuoka, 814-0180, Japan
SOURCE: Hypertension (2000), 36(4), 638-641
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 25 refs. The renin-angiotensin system has been studied and recognized as one of the major blood pressure-regulating systems for the past century. In the last quarter century, however, many alternative pathways of angiotensin II formation have been found, and among them, chymase has been a focus of interest because of its specificity and potency in the human cardiovascular system. Chymase evidently is not involved in functional regulation of blood pressure at least in the short term, but evidence is accumulating that it may be involved in structural remodeling of the cardiovascular system. The authors found increased **vascular** chymase activity in atherosclerotic lesions of the human aorta as well as in cardiac remodeling after myocardial infarction. The authors found a significant pos. correlation between serum total or LDL cholesterol levels and arterial chymase-dependent angiotensin II-forming activity in patients who were undergoing coronary artery bypass operation, suggesting that high serum cholesterol may trigger upregulation of **vascular** chymase and facilitate the development of atherosclerosis. This hypothesis was tested in Syrian hamsters fed a high cholesterol diet contg. 0.5% cholesterol: a marked **lipid** deposition in the aortic cusp developed and the plasma cholesterol levels were pos. correlated with aortic chymase activity. An orally active nonpeptide **chymase inhibitor** almost canceled this **lipid** deposition. These clin. and exptl. data indicated an

assocn. between cholesterol and **vascular** chymase upregulation that may facilitate the development of atherosclerosis.
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 20 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:422773 CAPLUS
DOCUMENT NUMBER: 133:131309
TITLE: Identification of domains in apoA-I susceptible to proteolysis by mast cell chymase: implications for HDL function
AUTHOR(S): Lee, Miriam; Uboldi, Patrizia; Giudice, Daniela; Catapano, Alberico L.; Kovanen, Petri T.
CORPORATE SOURCE: Wihuri Research Institute, Helsinki, 00140, Finland
SOURCE: Journal of Lipid Research (2000), 41(6), 975-984
CODEN: JLPRAW; ISSN: 0022-2275
PUBLISHER: Lipid Research, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB When stimulated, rat serosal mast cells degranulate and secrete a cytoplasmic neutral protease, chymase. The authors studied the fragmentation of apolipoprotein (apo) A-I during proteolysis of HDL3 by chymase, and examd. how chymase-dependent proteolysis interfered with the binding of 8 murine monoclonal antibodies (Mabs) against functional domains of apo A-I. Size exclusion chromatog. of HDL3 revealed that proteolysis for up to 24 h did not alter the integrity of the .alpha.-migrating HDL, whereas a minor peak contg. particles of smaller size with pre.beta. mobility disappeared after as little as 15 min of incubation. At the same time, generation of a large (26 kDa) polypeptide contg. the N-terminus of apoA-I was detected. This large fragment and other medium-sized fragments of apoA-I produced after prolonged treatment with chymase were found to be assocd. with the .alpha.HDL; meanwhile, small **lipid**-free peptides were rapidly produced. Incubation of HDL3 with **chymase inhibited** binding of Mab A-I-9 (specific for pre.beta.1HDL) most rapidly (within 15 min) of the 8 studied Mabs. This rapid loss of binding was paralleled by a similar redn. in the ability of HDL3 to induce high-affinity efflux of cholesterol from macrophage foam cells, indicating that proteolysis had destroyed an epitope that is crit. for this function. In sharp contrast, prolonged degrdn. of HDL3 by chymase failed to reduce the ability of HDL3 to activate lecithin-cholesterol acyltransferase (LCAT), even though it led to modification of 3 epitopes in the central region of apoA-I that are involved in LCAT activation. This differential sensitivity of the 2 key functions of HDL3 to the proteolytic action of mast cell chymase was compatible with the notion that, in reverse cholesterol transport, intactness of apoA-I is essential for pre.beta.1HDL to promote the high-affinity efflux of cellular cholesterol, but not for the .alpha.-migrating HDL particles to activate LCAT.
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 21 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:384173 CAPLUS
DOCUMENT NUMBER: 133:3766
TITLE: Isolation of SF2809-I, II, III, IV, V and VI substances exhibiting **chymase-inhibiting** activities from Dactylosporangium
INVENTOR(S): Tani, Masato; Gyobu, Yasuhiro; Moriyama, Chieko; Sasaki, Toru; Takenouchi, Osami; Kawamura, Takashi; Kamimura, Takashi; Harada, Toshiaki
PATENT ASSIGNEE(S): Meiji Seika Kaisha, Ltd., Japan; Teijin Ltd.
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2

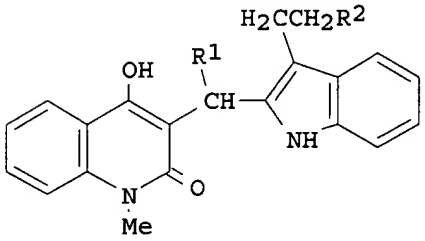
09/ 869,360

DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000032587	A1	20000608	WO 1999-JP6738	19991201
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1136488	A1	20010926	EP 1999-973023	19991201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6432978	B1	20020813	US 2001-857037	20010531

PRIORITY APPLN. INFO.: JP 1998-341523 A 19981201
WO 1999-JP6738 W 19991201

GI



I

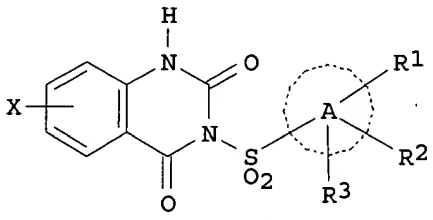
AB Novel compds. exhibiting **chymase-inhibiting** activities and being useful as various drugs, i.e., SF2809-I, SF2809-II, SF2809-III, SF2809-IV, SF2809-V and SF2809-VI substances represented by general formula [I; wherein R1 is hydrogen, Ph or p-hydroxyphenyl; and R2 is acetylamino (NHCOCH3) or hydroxyl] or pharmaceutically acceptable salts thereof are isolated from fermn. broth of Dactylosporangium. They are useful for the treatment or prevention of myocardial infarction, cardiac hypertrophy, cardiomyopathy, arteriosclerosis, hypertension, endovascular thickening, peripheral circulation disorders, kidney failure, inflammation, allergies, atopic dermatitis, rheumatism, asthma, and bronchitis. Thus, Dactylosporangium was aerobically cultured in a medium contg. glucose 2.0, sol. starch 1.0, soybean meal 1.5, polypeptone 0.1, wheat germ 0.8, staminol 0.1, NaCl 0.1, and CaCO3 0.2 (adjusted to pH 8.0 with 6 N NaOH) with stirring at 28.degree. for 5 days. The fermn. liq. (120 L) was centrifuged to sep. the microorganism. The supernatant liq. was extd. with EtOAc. The microorganism was extd. with 50% acetone and the acetone was distd. out from the filtrate under reduced pressure, followed by extn. with EtOAc. The combined EtOAc ext. was concd. in vacuo to give 56 g ext. which was washed with hexane, dissolved in MeOH, and purified by chromatog. using Sephadex LH-20 and Cosmosil column and HPLC to give SF2809-I 2.3, SF2809-II 1.3, SF2809-III 2.3, SF2809-IV 2.7, SF2809-V 1.1 and SF2809-VI 1.0 mg. The combined ext. was. SF2809-I, II, III, IV, V and VI showed IC50 of 7.3.times.10-6, 4.1.times.10-8, 2.1.times.10-6, 8.1.times.10-8, 4.3.times.10-8, 4.3.times.10-8, and 1.4.times.10-8 M against human chymase.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

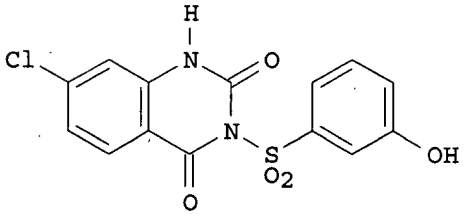
L2 ANSWER 22 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:144865 CAPLUS
DOCUMENT NUMBER: 132:180595
TITLE: Preparation of quinazoline derivatives as **chymase inhibitors**
INVENTOR(S): Fukami, Harukazu; Ito, Akiko; Imajo, Seiichi
PATENT ASSIGNEE(S): Suntory Limited, Japan
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000010982	A1	20000302	WO 1999-JP4503	19990820
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2341357	AA	20000302	CA 1999-2341357	19990820
AU 9953037	A1	20000314	AU 1999-53037	19990820
EP 1114035	A1	20010711	EP 1999-938565	19990820
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002523404	T2	20020730	JP 2000-566256	19990820

PRIORITY APPLN. INFO.: JP 1998-235633 A 19980821
WO 1999-JP4503 W 19990820
OTHER SOURCE(S): MARPAT 132:180595
GI



I



II

AB The title compds. [I; A = aryl; R1 = OH, NH2, alkylamino, etc.; R2, R3 = H, alkyl, halo, etc.; X = H, alkyl, alkoxy, etc.] which have a

chymase inhibitory activity and suppress the exacerbation of **vascular** permeability induced by chymase, were prepd. and formulated. E.g., a 3-step synthesis of II which showed IC50 of 0.36 .mu.M against chymase, was given.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 23 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:95832 CAPLUS
DOCUMENT NUMBER: 132:274101
TITLE: Inhibition of chymase reduces **vascular** proliferation in dog grafted veins
AUTHOR(S): Takai, S.; Yuda, A.; Jin, D.; Nishimoto, M.; Sakagichi, M.; Sasaki, S.; Miyazaki, M.
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki City, Osaka, Japan
SOURCE: FEBS Letters (2000), 467(2,3), 141-144
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We investigated the effect of a **chymase inhibitor** Suc-Val-Pro-PheP(OPh)2 on the proliferation of the grafted vein in dog. By 28 days after the operation, the mean intimal area of the grafted vein in the placebo group was 3.24.+-.0.32 mm2. The intimal area of the grafted vein in the **chymase inhibitor**-treated group was reduced to 63.9%. In the placebo group, the activities of chymase and angiotensin-converting enzyme in grafted vein were significantly increased 15- and 2-fold, resp. In the **chymase inhibitor** -treated group, chymase activity in the grafted veins was decreased significantly. These findings suggest that inhibition of chymase appears useful for preventing **vascular** proliferation.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 24 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:529171 CAPLUS
DOCUMENT NUMBER: 131:144615
TITLE: Preparation of 2-(3,4-dihydro-4-oxopyrimidin-3-yl)acetamide derivatives as **chymase inhibitors**
INVENTOR(S): Ishida, Koichi; Suzuki, Yoshikazu
PATENT ASSIGNEE(S): Nippon Kayaku Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9941277	A1	19990819	WO 1999-JP657	19990216
W: AU, CA, CN, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2321146	AA	19990819	CA 1999-2321146	19990216
AU 9924407	A1	19990830	AU 1999-24407	19990216
AU 744739	B2	20020228		
EP 1055683	A1	20001129	EP 1999-903924	19990216
R: CH, DE, ES, FR, GB, IT, LI, SE				
US 6300337	B1	20011009	US 2000-601808	20000808

PRIORITY APPLN. INFO.: JP 1998-50038 A 19980217

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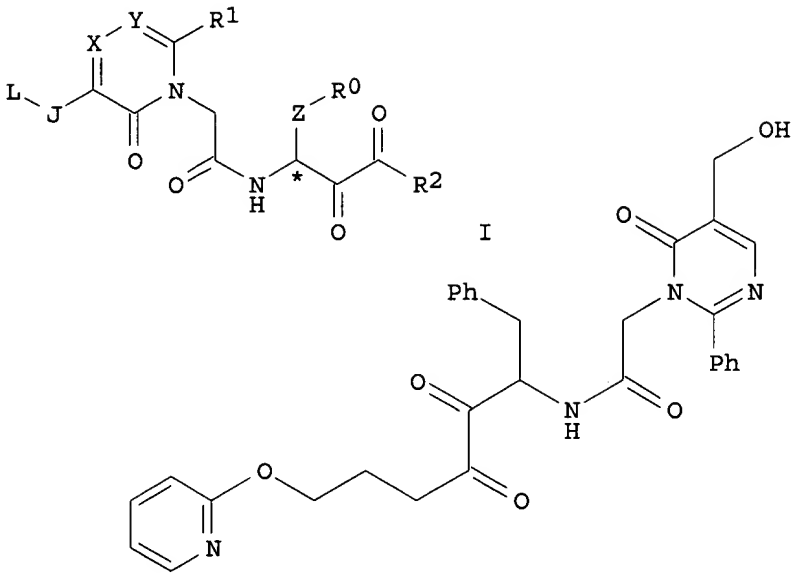
WO 1999-JP657 W 19990216

OTHER SOURCE(S): MARPAT 131:144615

GI



I

II

AB Novel acetamide derivs. represented by formula (I; R0 represents a substituted or non-substituted Ph group; R1 represents an aryl, a heteroaryl or an aliph. lower alkyl group with or without a substituent; R2 represents a substituted or non-substituted alkyl, arylalkyl, heteroarylalkyl or heteroaryloxyalkyl or aryl; J represents a carbonyl or substituted or non-substituted methylene group; L represents a substituted or non-substituted amino or hydroxy; X and Y independently represent a nitrogen atom or a carbon atom; and Z represents a methylene group or a polyethylene group optionally having a substituent] are prepd. These compds. have inhibition activity for a chymotrypsin type protease and are useful as inhibitors for the above enzyme, esp. as inhibitors for chymase, and as medicines, e.g., an antiasthmatic, antiinflammatory, antirheumatic, or antihypertensive drug, or a drug for treating heart failure, myocardial infarction, cardiac hypertrophy, nephritis, kidney failure, or injury of a blood **vessel** combined with atheroma or angioplasty. Thus, 5-acetyloxymethyl-2-phenyl-3,4-dihydropyrimidin-4-one-3-ylacetic acid (prepn. given) was condensed with 2-amino-3-hydroxy-4-oxo-1-phenyl-7-(2-pyridyloxy)heptane p-toluenesulfonic acid salt using 1-hydroxybenzotriazole and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride in THF and DMF at room temp. overnight, followed by oxidn. with DMSO, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, and pyridinium trifluoroacetate in CH2Cl2 and deacetylation with 3 N aq. HCl at room temp. overnight to give the title compd. (II). II showed IC50 of 22 and 2.0 .mu.M against human and dog chymase, resp.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 25 OF 31 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:396317 CAPLUS

DOCUMENT NUMBER: 131:194787

TITLE: Angiotensin-converting enzyme-independent contraction to angiotensin I in human resistance arteries

AUTHOR(S): Padmanabhan, Neal; Jardine, Alan G.; McGrath, John C.; Connell, John M. C.

CORPORATE SOURCE: Department of Medicine and Therapeutics, Western

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Infirmary, University of Glasgow, Glasgow, UK
SOURCE: Circulation (1999), 99(22), 2914-2920
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In vitro studies of myocardial tissue suggest that angiotensin II (Ang II) may be generated by both ACE and chymase. A similar dual pathway may exist in the vasculature. We studied the effects of ACE and **chymase inhibitors** on the contractile response to angiotensin I (Ang I) in human resistance arteries to investigate ACE-independent generation of Ang II. The s.c. resistance arteries (250 to 350 .mu.m) were obtained from gluteal biopsies from volunteers and New Zealand White rabbits and mounted on a wire myograph. Contractile ability was tested with high-potassium depolarization and norepinephrine 10 .mu.mol/L and endothelial integrity by relaxation to acetylcholine 3 .mu.mol/L. Cumulative concn.-response curves were constructed for Ang I in the presence of enalaprilat 1 .mu.mol/L, chymostatin 10 .mu.mol/L, or both inhibitors together. In the rabbit, enalaprilat completely inhibited the Ang I response. In human **vessels**, enalaprilat or chymostatin alone had no effect, but the combination of enalaprilat and chymostatin almost completely inhibited the response to Ang I. A dual pathway for Ang II generation exists in human resistance arteries, mediated by ACE and a chymostatin-sensitive enzyme, probably chymase. We confirm that a marked species difference exists in the mechanism of Ang II generation between the human and the rabbit. More efficacious suppression of the renin-angiotensin system may require development of novel enzyme inhibitors or combinations of currently available drugs.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 26 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:680934 CAPLUS
DOCUMENT NUMBER: 130:20951
TITLE: Alternative pathways of angiotensin II production in the human saphenous vein
AUTHOR(S): Borland, Julie A. A.; Chester, Adrian H.; Morrison, Karen A.; Yacoub, Magdi H.
CORPORATE SOURCE: Department of Cardiothoracic Surgery, National Heart and Lung Institute, Imperial College of Science Technology and Medicine, Heart Science Centre, Harefield Hospital, Uxbridge, UK
SOURCE: British Journal of Pharmacology (1998), 125(3), 423-428
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of this study was to demonstrate the existence, location and functional importance of an alternative angiotensin II-forming pathway other than angiotensin converting enzyme (ACE) in the human saphenous vein (SV). **Vascular** reactivity studies using an in vitro organ bath technique showed that the SV produced similar max. contractions in response to angiotensin I (41.5 mN) compared to those obsd. to angiotensin II (46.7 mN). The response to angiotensin I could be significantly inhibited by incubation with the AT1 receptor antagonist losartan (1 .mu.M). Prior incubation of segments of SV with either captopril (1 .mu.M), quinaprilat (1 .mu.M), or the **chymase inhibitor** soybean trypsin inhibitor (SBTI) (10 .mu.M) singularly failed to have any inhibitory effect on the response to angiotensin I. However when **vessel** segments were coincubated with quinaprilat (1 .mu.M) and SBTI (10 .mu.M), the SV exhibited a rightward shift in curve profile to angiotensin I and a markedly reduced max. response 12.5 mN, when compared

to control (30.4 mN), quinaprilat (24.5 mN), and SBTI (31.6 mN) on their own. An immunohistochem. technique employing streptavidin biotin peroxidase localized ACE to both endothelial cells and smooth muscle cells while chymase was confined to mast cells in the adventitia of the **vessel** wall. In conclusion, the results demonstrate the existence of an alternative angiotensin I converting pathway to that of ACE, involving chymase. Therefore, there is the capacity for a continuation of angiotensin II formation. in the presence of ACE inhibition.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 27 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:576827 CAPLUS
DOCUMENT NUMBER: 129:214502
TITLE: Angiotensin II formation by chymase in the cardiovascular tissue
AUTHOR(S): Okunishi, Hideki
CORPORATE SOURCE: Dep. Pharmacol., Shimane Med. Univ., Izumo, 693-8501, Japan
SOURCE: Nippon Yakurigaku Zasshi (1998), 112(3), 203-212
CODEN: NYKZAU; ISSN: 0015-5691
PUBLISHER: Nippon Yakuri Gakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review with 50 refs. Angiotensin-converting enzyme (ACE) inhibitors attenuated the contractile responses to angiotensin (Ang) I of arterial strips of humans, monkeys, and dogs, as can be expected. Unexpectedly, however, the response was not abolished by sufficient doses of ACE inhibitors, the facts suggesting the Ang I conversion by a non-ACE enzyme(s). HPLC anal. of the incubation product of Ang I with **vascular** tissues revealed that Ang II was yet formed despite complete ACE inhibition, and the ACE inhibitor-insensitive Ang II formation was blocked by chymostatin. The disclosed Ang II-forming enzyme was identified as chymase, which was later found in abundance in the human heart. Another notable discovery by us is the species difference in chymase processing of Ang I: chymases of the primates, dog, and hamster convert Ang I to Ang II, while chymases of rat, rabbit, and probably mouse do not. Accumulating evidence indicating that Ang II is not merely a vasopressor agent but also a growth-promoting factor, which leads to tissue hypertrophy and fibrosis, together with the results our studies lead us to propose the tissue-remodeling roles of chymase formed Ang II in various cardiovascular diseases: dog neointimal proliferation after angioplasty, hamster cardiomyopathy, etc., in which chymase mRNA is increased concordantly with tissue remodeling. The fact that Ang II receptor antagonists, not ACE inhibitors, suppress the tissue remodeling supports our argument that Ang II is formed predominantly by chymase in diseased tissues. Orally active **chymase inhibitors**, evolving in our study, should help explore the actual roles of chymase as well as the rational treatment of tissue-remodeling disorders.

L2 ANSWER 28 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:288415 CAPLUS
DOCUMENT NUMBER: 128:290021
TITLE: Inhibitory effects of tranilast on neointima formation in canine balloon-injured carotid arteries: pathophysiological functions of chymase-dependent angiotensin II
AUTHOR(S): Mikoshiba, Imao
CORPORATE SOURCE: Dep. Pharmacology, Osaka Med. College, Takatsuki, Japan
SOURCE: Osaka Ika Daigaku Zasshi (1997), 56(3), 62-74
CODEN: OIDZAU; ISSN: 0030-6118
PUBLISHER: Osaka Ika Daigaku Igakkai

09/ 869,360

DOCUMENT TYPE: Journal
LANGUAGE: Japanese

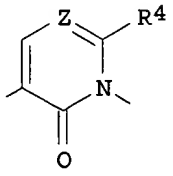
AB In addn. to the angiotensin converting enzyme (ACE)-dependent pathway, the chymase-dependent angiotensin (Ang)II-forming pathway plays a major role in myointimal proliferation following **vascular** injury, and the involvement of chymase is of interest in the mechanisms of restenosis after percutaneous transluminal coronary angioplasty (PTCA) in humans. Since chymase is primarily produced in mast cells and secreted into the interstitium, there is a possibility that the chymase-dependent Ang II-forming pathway may be inhibited by anti-allergic agents that suppress activation of mast cells. In the present study, we assessed the inhibitory effects of an anti-allergic agent, tranilast, on intimal thickening following balloon injury in the canine carotid artery, and we further investigated the possible roles of chymase and ACE, the two major **vascular** AngII-forming enzymes, in the pathogenesis of neointima formation. Five beagle dogs were treated with tranilast (50 mg/kg, twice daily, p. o.) and seven with placebo. After a two-week treatment period, a balloon catheter was inserted into the right common carotid artery to induce intimal injury, while the left common carotid artery was kept intact and used as an uninjured control. Following intimal injury, the dogs were treated with tranilast or placebo for another four weeks. Then, the animals were killed, and the injured and uninjured arteries were excised for pathol. anal. and measurement of chymase-like activity, ACE activity, and their mRNA levels. In the placebo group, marked intimal thickening was seen as a result of neointima formation in the injured arteries, and numerous mast cells appeared in adventitia. **Vascular** chymase-like activities and chymase mRNA levels in the injured arteries were 10.2-fold and 4.8-fold, resp., compared with those of the uninjured arteries were 10.2-fold and 4.8-fold, resp., compared with those of the uninjured arteries. **Vascular** ACE activities were slightly increased in the injured arteries, while **vascular** ACE mRNA levels did not differ between injured and uninjured arteries. In the tranilast-treated group, neointima formation was significantly suppressed in the injured arteries, and the no. of adventitial mast cells was significantly decreased. **Vascular** chymase-like activities in the injured arteries were completely suppressed, and chymase mRNA levels were reduced by 56.7%. However, **vascular** ACE activities and mRNA levels were not affected by chronic treatment with tranilast. These results demonstrate that chymase-dependent Ang II plays a more important role in intimal thickening in balloon-injured arteries than ACE-dependent Ang II. Tranilast is effective for the prevention of neointima formation following balloon injury, and inhibition of the chymase-dependent Ang II-forming pathway is implicated in the mechanisms of this action.

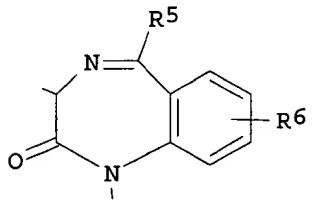
L2 ANSWER 29 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:126655 CAPLUS
DOCUMENT NUMBER: 128:192666
TITLE: Preparation of acetamides, their use as **chymase inhibitors** and angiotensin II inhibitors, and cardiovascular agents containing them
INVENTOR(S): Akaha, Atsushi; Takenaka, Kohei; Itani, Hiromichi; Sato, Akihiro; Nakanishi, Isao
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 12 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

JP 10053579	A2	19980224	JP 1997-160803	19970618
PRIORITY APPLN. INFO.:			AU 1996-626	19960624
OTHER SOURCE(S):	MARPAT 128:192666			

GI

Q1 = 

Q2 = 

AB R1NHXYCONHCHR2COR3 I [R1 = H, protecting group; R2 = ar(lower)alkyl; R3 = lower haloalkyl, (protected) CO2H; X = Q1, Q2; R4, R5 = halo-, lower alkoxy-, or Ph-substituted aryl, cyclo(lower)alkyl; R6 = H, lower alkyl; Z = N, CH; Y = lower alkylene] or their salts, useful for prevention or treatment of heart and/or circulation disorders, are prepd. by oxidn. of R1aNHXYCONHCHR2CHR3OH (R1a = protecting group; R2, R3, X, Y = same as above) or their salts, followed by optional deprotection. Oxidn. of 905 mg 2-[5-[(benzyloxycarbonyl)amino]-2-(4-fluorophenyl)-1,6-dihydro-6-oxo-1-pyrimidinyl]-N-[2-(4,4,4-trifluoro-3-hydroxy-1-phenyl)butyl]acetamide with 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-1-(1H)-one at room temp. for 15 h in CH2Cl2 gave 644 mg the corresponding ketone deriv., which inhibited chymase at IC50 of <1.0 .times. 10-5 M.

L2 ANSWER 30 OF 31 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	1994:631372 CAPLUS
DOCUMENT NUMBER:	121:231372
TITLE:	Preparation of peptide inhibitors of angiotensin I chymase(s) including human heart chymase
INVENTOR(S):	Hoover, Dennis J.
PATENT ASSIGNEE(S):	Pfizer Inc., USA
SOURCE:	PCT Int. Appl., 87 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9325574	A1	19931223	WO 1993-US3625	19930423
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 644892	A1	19950329	EP 1993-909587	19930423
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				

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PRIORITY APPLN. INFO.: US 1992-897723 19920612
WO 1993-US3625 19930423

OTHER SOURCE(S): MARPAT 121:231372

AB R4ADCHR3COXNHCHY[(CH2)nR1] [R1 = (substituted) Ph, naphthyl, cycloalkyl, (benzo-fused) unsatd. heterocyclyl; R3 = (substituted) alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylthioalkyl, Ph, unsatd. heterocyclyl(alkyl), phenylalkyl; R4 = (substituted) piperazino, piperidino, pyrrolidino, 3-azabicyclo[3.1.0]hex-3-yl, azetidino, 4-morpholino, 4-thiomorpholino, 1-oxothiomorpholino, 1,1-dioxothiomorpholino, alkyl, cycloalkyl, etc.; A = CO, SO2; D = (alkyl)imino, (alkyl)methylene, O, CH(OH); X = (substituted) proline, 2-piperidinecarboxylic acid, 2-azetidinecarboxylic acid residue; Y = BF2, B(OM)2, COZ, C(OH)2Z; M = H, alkyl; B(OM)2 = satd. heterocyclyl; Z = CF2R11, CF2CONR12R13, CO2R12, (substituted) heterocyclyl; R11 = H, F, alkyl, perfluoroalkyl, aminoalkyl, alkylaminoalkyl, alkoxyalkyl, hydroxyalkyl; R12, R13 = H, alkyl, alkenyl, etc.], were prepd. Title compds. are effective for treating or preventing hypertension, congestive heart failure, myocardial infarction, cardiac and left ventricular hypertrophy, coronary artery disease including myocardial infarction, **vascular** hypertrophy, and **vascular** damage following diabetic and non-diabetic renal disease, and **vascular** damage assocd. with angioplasty and aetheroma (no data). Thus, N-[(1,1-dimethylethoxy)carbonyl]phenylalanyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]prolinamide was prepd. in several steps from 3(S,R)-N-[(1,2-dimethylethoxy)carbonyl]-3-amino-2-hydroxy-4-phenylbutyronitrile.

L2 ANSWER 31 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:609610 CAPLUS
DOCUMENT NUMBER: 113:209610
TITLE: Anaphylatoxin binding and degradation by rat peritoneal mast cells. Mechanisms of degranulation and control
AUTHOR(S): Fukuoka, Yoshihiro; Hugli, Tony E.
CORPORATE SOURCE: Dep. Immunol., Res. Inst. Scripps Clin., La Jolla, CA, 92037, USA
SOURCE: Journal of Immunology (1990), 145(6), 1851-8
CODEN: JOIMA3; ISSN: 0022-1767
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Incubation of radiolabeled human complement C3a with rat peritoneal mast cells resulted in high levels of uptake and extensive degrdn. of the ligand. Both cell-bound and free radiolabeled human C3a underwent extensive degrdn. by rat mast cells even at 0.degree.. The protease inhibitors PMSF, chymostatin, and soybean trypsin inhibitor were most effective in preventing radiolabeled human C3a degrdn. Degrdn. of the cell-bound ligand was totally inhibited only by PMSF. These compds. are effective inhibitors of a chymotrypsin-like enzyme (chymase) extd. from rat mast cells. Chem. crosslinking of radiolabeled human C3a to surface components on the rat mast cells, in the presence of PMSF, revealed one major and two minor bands. The mast cell component in both the major and minor bands proved to be chymase-assocd. based on a direct comparison with purified chymase isolated from rat mast cells. However, neither antichymase antibody nor **chymase inhibitors** influenced the degranulating activity of C3a on rat mast cells that occur independently of the C3a-chymase interactions. Therefore, there are neither specific C3a-binding sites on rat mast cells nor specific receptors whose occupancy leads to cellular activation. Although human C3ades Arg is inactive on guinea pig ileal and lung tissue, it binds to and induces degranulation of rat mast cells, as well as enhances **vascular** permeability in rat skin, at concns. nearly identical to that of intact C3a. The fact that both C3a and C3ades Arg stimulated mast cell activation, at concns. in excess of 10-6 M, argues against specific

binding sites for the anaphylatoxin on rat mast cells. It is proposed that the cationic C3a mol. activates rat mast cells in a secretory and nonlytic manner by a nonspecific mechanism similar to that of other polybasic compds.

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FILE 'CAPLUS' ENTERED AT 11:17:58 ON 31 MAR 2003
L1 179 S CHYMASE INHIBIT?
L2 31 S L1 AND (VASCULAR? OR LIPID? OR VESSEL?)

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